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54	TITLE OF INVENTION

Process for the preparation of pellets with a content of up to 90 wt. % of a pharmaceutical active ingredient

Patent application by Grünenthal GmbH, D-52078 Aachen
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Process for the preparation of pellets with a content of up to 90 wt.% of a pharmaceutical active ingredient

The present invention relates to a process for the preparation of pellets with a content of up to 90 wt.% of a pharmaceutical active ingredient having an extremely high solubility in water, by aqueous moist extrusion and subsequent spheronisation.

Extrusion and subsequent spheronisation is a long-known method for the preparation of granules having a defined shape and particle size which has also gained great importance in the production of pharmaceutical pellets (J.W. Conine et al., Drug & Cosmetic Ind. 106, 38-41 (1970)). At the same time the processing of numerous pharmaceutical active ingredients has also been described, as such multiparticulate forms of administration, owing to an improved bioavailability, pharmaceutical safety and reliability of action, are often preferred to the monolithic forms of dosage. Moreover, there is comprehensive literature dealing with the optimisation of the conditions of preparation, with the effect of the composition of the formulation and with the differences between various types of extruder as well as with the principles of extrusion/spheronisation (L. Hellen et al., Int. J. Pharm., 95, 197-204 and 205-216 (1993); L. Baert et al., Int. J. Pharm., 96, 225-229 (1993) and Int. J. Pharm., 81, 225-223 (1992) and Int. J. Pharm. 97, 79-92 (1993); K. Thoma et al., Drug Dev. Ind. Pharm., 24 (5), 401-411 (1998)).

The advantage of extrusion/spheronisation for the preparation of pellets over pelletising is, among other factors, a greater compression of the pellets. Because of

that, homogeneous pellets having a high content of active ingredients, that is, a content of active ingredients of up to 90 wt.%, can be obtained by the aforementioned method. Moreover, the pellets prepared by extrusion/spheronisation are not only denser, but the surface of the pellet also has a lower porosity, so that the applied quantity for functional films can be distinctly decreased and more even release profiles can be achieved (G. Zhang et al., Drug Dev. Ind. Pharm., 16 (7), 1171-1184 (1990)). For this reason the preferred method for the preparation of pellets, in particular for the preparation of highly-dosed pellets which are provided with coatings having controlled-release action, is by extrusion/spheronisation.

Besides the so-called melt extrusion, extrusion of granules moistened with water is one of the commonest extrusion methods. Here the active ingredients together with the auxiliary substances are granulated with the addition of water and then extruded, before the extrudates are rounded in a spheroniser and dried. This method has the advantage over melt extrusion that undesirable heat load on the mixtures containing the active ingredients is avoided.

Whereas pellets having a high content of active ingredients of up to 90 wt.%, even for active ingredients with a good to very good solubility in water, can be prepared by melt extrusion (WO 96/14059), the limit to the content of active ingredients in pellets prepared by the aqueous extrusion methods depends quite crucially on the degree of water-solubility of the active ingredient. Thus, for example, for active ingredients having low to poor solubility in water, pellets with contents of active ingredients of more than 80 wt.% are described, the pellets still being sufficiently round and having a narrow particle size distribution despite the low content of auxiliary substances (G.A. Hileman et al., Drug Dev. Ind. Pharm., 19 (4), 483-491 (1993)). However, it is recognised technical knowledge that

the better the water-solubility of the active ingredients, the lower the quantity of active ingredient which can be incorporated into the pellets (J.M. Newton et al., Pharm. Research, 509-514 (1998); P.H. Harrison, J. Pharm. Pharmacol., 37, 686-691 (1985)). Accordingly, in the case of readily water-soluble active ingredients having a solubility in water of 0.3 g/ml, generally only pellets having a content of active ingredients of 60 wt.% at most can be prepared well by means of aqueous moist extrusion.

Accordingly, the object of the present invention was to provide pellets containing very highly water-soluble, pharmaceutical ingredients, that is, those having a solubility in water of ≥ 0.5 g/ml, preferably ≥ 1 g/ml, which pellets are prepared by means of the aqueous moist extrusion process and, advantageously, have not only a defined particle size and very good roundness, but also a relatively narrow particle size spectrum.

This object is achieved by the process according to the invention for the preparation of pellets containing ≥ 50 wt.% of a pharmaceutical active ingredient having a solubility in water of ≥ 0.5 g/ml, by granulating the mixture containing the active ingredient with water, extrusion, rounding and drying of the moist pellets, which is characterised in that the mixture containing the active ingredient consists of

A) at least 50 wt.%, preferably at least 65 wt.%, of at least one active ingredient having a solubility in water of > 0.5 g/ml, preferably > 1 g/ml, and

B) at most 50 wt.%, preferably at most 35 wt.%, of the combination of

   a) microcrystalline cellulose having an average particle size of 15 to 25 µm, determined by laser diffraction (Malvern Master Sizer)

and

b) low-substituted hydroxypropyl cellulose having an average particle size in the range of 10 to 25 µm, measured by means of laser diffraction,

the weight ratio of a):b) being in the range of 4:6 to 6:4 and the amount of water worked into the mixture being only so much that the latter has an adequate plasticity for the extrusion and spheronisation.

By means of the process according to the invention it is possible to prepare pellets containing up to 90 wt.% of an active ingredient having extremely high solubility in water, that is, a solubility in water of at least 0.5 g/ml, such as, for example, tramadol hydrochloride (> 3.0 g/ml), chlorpromazine hydrochloride (2.5 g/ml), metamizol-Na (> 1 g/ml), diphenhydramine hydrochloride (860 mg/ml).

It is essential to the process according to the invention that the auxiliary substances used, namely, microcrystalline cellulose and low-substituted hydroxypropyl cellulose, have a certain average particle size and are used in a certain weight ratio to one another. Thus one must use a microcrystalline cellulose having an average particle size of 15 to 20 µm, such as, for example, Avicel™ PH 105 or Emcocel SP 15™, or low-substituted hydroxypropyl cellulose having an average particle size in the range of 10 to 25 µm, such as, for example, 1-HPC LH 31™, 1-HPC LH 32™ or 1-HPC LH 41™, preferably having a particle size of ≤ 20 µm (for example, 1-HPC LH 32™, 1-HPC LH 30™ or 1-HPC LH 41™) and a hydroxypropyl content of 10 to 13 wt.% (1-HPC LH 31).

The comparison tests show that when the hitherto preferably used microcrystalline cellulose having a particle size of approximately 50 µm is used in the preparation, by moist

extrusion, of pellets containing very readily water-soluble active ingredients, such as tramadol hydrochloride, only pellets with a content of active ingredients of at most 40 to 45 wt.% can be prepared in useful yield. Agglomeration or scarcely roundable rods of extrudate (dumb-bells) having a high dust content depending on the quantity of water is the result at higher contents of active ingredients. Surprisingly, this disadvantage can successfully be surmounted by the auxiliary substances used according to the invention.

The proportion of these auxiliary substances in the mixture containing active ingredients should be 10 to 50 wt.%, preferably from 20 to 30 wt.%, and a ratio of microcrystalline cellulose to low-substituted hydroxypropyl cellulose of 4:6 to 6:4, preferably 1:1, particularly preferably 5.1:4.9, should be maintained.

The person skilled in the art is familiar with the remaining conditions of the process, such as the adjustment of the duration, speed and loading during the spheronisation depending on the moisture content of the extrudates, the choice of the type of extruder and the spheronisation conditions.

The pellets prepared by the process according to the invention in the first place have no controlled-release action for the incorporated highly water-soluble active ingredients. However, despite the high tendency of low-substituted hydroxypropyl cellulose to disintegrate, the pellets show no disintegration even after release of the active ingredient and residence for several hours in physiological release media. They are therefore ideal substrates to be covered with functional coatings such as, for example, coatings having controlled-release action and/or coatings which are resistant to gastric juices. It is also possible to mould the coated pellets to form

rapidly disintegrating tablets, perhaps in combination with uncoated pellets as an initial dose. The advantage of the formulation lies in the incorporation of high quantities of active ingredients despite their high solubility in water. Because of this, high dosages of the incorporated active ingredient can be administered in the form of small capsules or tablets, which are generally more pleasant for the patients to take.

The invention accordingly also provides processes for the preparation of pellets having coatings having controlled-release action and/or which are resistant to gastric juices, optionally moulded to form tablets or enclosed in capsules, by providing the pellets prepared according to the invention with appropriate coatings after preparation.

All pharmaceutically safe coating materials which are known to the person skilled in the art are suitable for use as coating materials. Preferably natural, optionally modified or synthetic polymers are used as coating materials. These are polymers such as, for example, cellulose ethers or acrylic resins. Cellulose derivatives which are insoluble in water or swellable in water are most preferred, such as alkyl cellulose, preferably ethyl cellulose, or acrylic resins which are insoluble in water, such as poly(meth)acrylic acid and/or its derivatives, such as its salts, amides or esters. Waxes which are insoluble in water can also be used as coating material.

These materials are known from prior art, for example, Bauer, Lehmann, Osterwald, Rothgang, "Überzogene Arzneiformen", Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1998, page 69 ff. and are herewith introduced as a reference.

In addition to the polymers and waxes which are insoluble in water, optionally in order to adjust the release rate of

the active ingredient, concomitant use may also be made of preferably up to 30 wt.% of preferably water-soluble polymers without controlled-release action, such as, for example, polyvinylpyrrolidone, or water-soluble cellulose derivatives, such as hydroxyethyl cellulose, hydroxypropyl methyl cellulose or hydroxypropyl cellulose, optionally in combination with known plasticisers.

The formulations containing active ingredients may also be provided with further coatings in addition to the coating having controlled-release action.

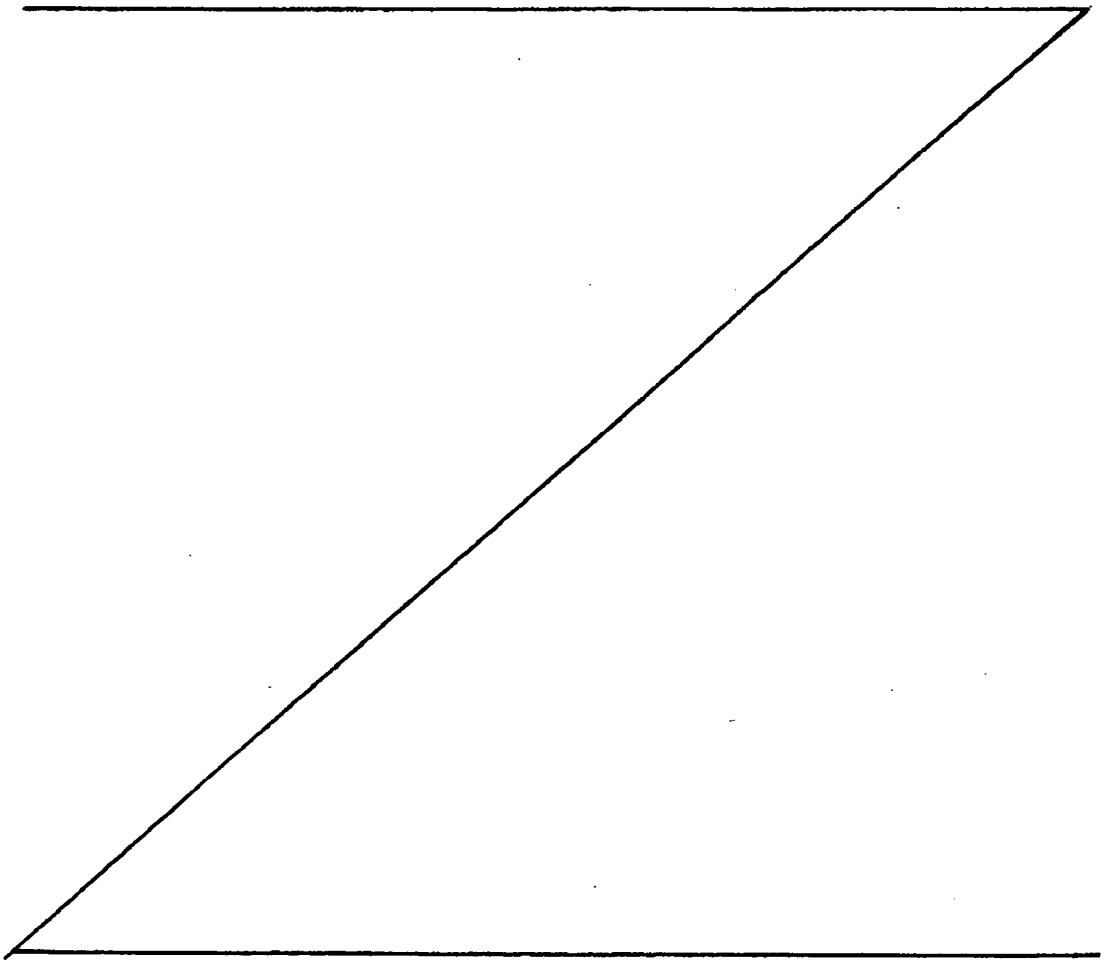
In this connection, for example, such a coating composed of a material which is different from the material of the coating having controlled-release action can be applied to the substrate surface as a separating layer without controlled-release action.

Suitable covering materials for this separating layer are preferably cellulose, polyvidones, polyacrylates or even natural polymeric materials.

It is also possible to make the further coating - preferably over the coating having controlled-release action - out of the active ingredient of the substrates or out of an active ingredient which is different from these, from which this active ingredient can be released uncontrolled after oral administration. By means of this multilayered coating, after the administration of the preparation an initial dose can be made available very rapidly for the initial therapy, with the level of the active ingredient being held through the subsequent controlled-release administration of the active ingredient. Suitable coating materials for this are pharmaceutically safe materials in combination with the initial active ingredient such as, for example, cellulose ethers, polyvidones or polyacrylates. But it is also possible to

provide in the coating without controlled-release action, in addition to or instead of the substrate active ingredient or of the pharmaceutically active ingredient which is different from this.

In addition, besides the coating having controlled-release action, the pellets may also have other coatings whose solubility is pH-dependent. Thus, for example, it can be ensured that at least a proportion of the pellets of a preparation pass through the gastric tract without being released and that the active ingredients are first released in the intestinal tract.



Examples

Example 1

Preparation of tramadol hydrochloride pellets with a content of active ingredients of 55 wt.%

microcrystalline cellulose with an average particle size of 20 µm (Avicel PH 105)	1150 g
low-substituted hydroxypropyl cellulose (L-HPC LH 31) average particle size 20 µm	1100 g
Tramadol-HCl	2750 g

The active ingredient and the auxiliary substance were first of all mixed for 10 minutes in a Diosna P25 granulator and then granulated for 10 minutes with 2100 g purified water. The moist granular material was extruded in an extruder, model NICA E140, having a 1 x 2 mm die and was then rounded for 10 minutes in a spheroniser, model NICA S450, at 900 min^{-1} and with a loading of 3 kg in each case. The moist pellets were dried overnight at 45°C in a drying oven and then packaged.

The screen analysis was carried out using 100 g pellets in a vibrating screen tower from the firm Fritsch (10 min) and analytical screens having mesh sizes of 630 µm to 2000 µm. The residues on the individual screen decks were determined by weighing and the weights of the individual screen fractions were recorded as wt.% of the total sample. In each case the recorded fractions were the result of n = 3 screen analyses.

Screen fraction in µm	wt.%
<800	3
800 - 1250	94
1250 - 1400	3

The yield of round pellets having a particle size of 800 to 1250 µm was 94%.

Example 2

Preparation of tramadol hydrochloride pellets with a content of active ingredients of 70 wt.%

microcrystalline cellulose average particle size 20 µm (Avicel PH 105)	77.5 g
low-substituted hydroxypropyl cellulose average particle size 20 µm (l-HPC LH 31)	72.5 g
Tramadol-HCl	350.0 g

The pellets were prepared in a manner similar to Example 1, but mixing of the powder and granulation were carried out with 108 g purified water in a Kenwood Chef mixer. The sample was extruded using a 1.2 x 2.4 mm die and spheronised, the loading of the spheroniser being

approximately 600 g. The screen analysis of the pellets was carried out as in Example 1.

Screen fraction in µm	wt.%
<1000	1
1000 - 1600	98
1600 - 2000	1

The yield of round pellets having a particle size of 1000 to 1600 µm was 98%.

Example 3

Preparation of tramadol hydrochloride pellets with a content of active ingredients of 90 wt.%

microcrystalline cellulose (Emcocel SP 15) average particle size 15 µm	27.5 g
low-substituted hydroxypropyl cellulose average particle size 20 µm (1-HPC LH 31)	22.5 g
Tramadol-HCl	450.0 g

The granulation was carried out using 70 g purified water, otherwise the pellets were prepared and tested as in Example 2.

Screen fraction in µm	wt.%
<1000	2
1000 - 1600	90
1600 - 2000	8

The yield of round pellets having a particle size of 1000 to 1600 µm was 90%.

Example 4

Preparation of metamizol sodium pellets with a content of active ingredients of 80 wt.%

microcrystalline cellulose (Avicel PH 105) average particle size 20 µm	100.0 g
low-substituted hydroxypropyl cellulose average particle size 10 µm (l-HPC LH 41)	100.0 g
Metamizol-Na	800.0 g

The granulation was carried out using 200 g purified water; a 1 x 2 mm die was used for the extrusion and the loading of the spheroniser was 1200 g. Otherwise the pellets were prepared and tested as in Example 2.

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Screen fraction in µm	wt.%
<800	2
800 - 1250	95
1200 - 2000	3

The yield of round pellets having a particle size of 800 to 1250 µm was 95%.

Claims

1. Process for the preparation of pellets containing ≥ 50 wt.% of a pharmaceutical active ingredient having a solubility in water of ≥ 0.5 g/ml, by aqueous granulation of the mixture containing the active ingredient, extrusion, rounding and drying of the moist granules, characterised in that the mixture containing the active ingredient consists of

   A) at least 50 wt.% of at least one active ingredient having a solubility in water of > 0.5 g/ml

   B) at most 50 wt.% of the combination of

      a) a microcrystalline cellulose having an average particle size of 15 to 20 µm and

      b) a low-substituted hydropropyl cellulose having an average particle size in the range of 10 to 25 µm,

   the weight ratio of a):b) being in the range of 4:6 to 6:4 and the amount of water worked into the mixture being only so much that the latter has an adequate plasticity for the extrusion and spheronisation.

2. Process according to claim 1, characterised in that the weight ratio of a):b) is 1:1.

3. Process according to claim 1 or 2, characterised in that the active ingredient used is tramadol hydrochloride having a solubility in water of > 3.0 g/ml, metamizol-Na or diphenhydramine hydrochloride, each having a solubility in water of 1 g/ml.

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4. Process according to one or more of claims 1 to 3, characterised in that pellets with a content of active ingredients of up to 90 wt.% are prepared.

5. Process according to one or more of claims 1 to 4, characterised in that the pellets are provided with a coating having controlled-release action and/or a coating which is resistant to gastric juices.

6. Process according to one or more of claims 1 to 5, characterized in that the pellets are enclosed in capsules or moulded to form tablets.

7. Process according to claim 1, characterised in that the mixture contains at least 65 wt.% of component A) and at most 35 wt.% of the combination B).

8. A process according to claim 1, substantially as herein described and illustrated.

9. A new process for the preparation of pellets, substantially as herein described.

DATED THIS 17 DAY OF JANUARY 2000

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